REMARKS

Applicant respectfully requests reconsideration. Claims 28, 29, 31-33 and 36 were previously pending in this application. Claims 28, 29, 31-33 and 36 are amended herein to clarify that the oligonucleotide is immunostimulatory. No claims are canceled. Claims 28, 29, 31-33 and 36 are still pending for examination with claims 28 and 29 being independent claims. No new matter has been added.

Rejection Under 35 U.S.C. 103

Claims 28-29, 31-33 and 36 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kuramoto et al. 1992 Jpn J. Cancer Res Vol. 83 pgs. 1128-1131 in view of Goodchild et al. 1990 The American Chemical Society, Vol. 1, No. 3 pgs. 165-182, Hutcherson et al. U.S. Patent No. 5,723,335 March 3, 1998 (filed March 25, 1994), and Cheng et al. U.S. Patent No. 5,646,126 July 8, 1997 (filed February 29, 1994) is maintained for the reason set forth in the previous office action. The Office Action is divided into two sections, A: issues addressing a prima facie obvious rejection and B: issues related to the evidence provided by Applicant to rebut a prima facie rejection.

A. The Office has not made a prima facie rejection of the claims under 35 USC 103. The rejection is based on the assertion that it would have been obvious to the skilled artisan to modify an immunostimulatory oligonucleotide having a phosphodiester backbone based on the teaching in the art that an antisense oligonucleotide or the oligonucleotide of Hutcherson et al can be modified to improve stability.

The skilled artisan would not have been motivated to combine the Hutcherson et al and Kuramoto et al references simply because both describe immunostimulating compounds. Numerous immune stimulating compounds are known, including adjuvants, bacterial cell wall components, cytokines, plant extracts such as Echinacea to name a few. The immune system is complex. It is not prima facie obvious to combine any immune stimulating compound with another immune stimulating compound simply because both are immune stimulatory in the absence of additional reasons. They may function on completely unrelated aspects of the immune system or may even

stimulate aspects of the immune response that have differing effects on the body. In the instant case, neither reference provides any basis for the combination. The ODN of Kurumoto are phosphodiester ODN that are believed to be immunostimulatory as a result of the palindromic sequence. The ODN of Hutcherson are stated to have immune stimulating properties as a result of a phosphorothioate internucleotide linkage. The fact that the two compounds are immune stimulating is not sufficient to support the rejection.

B. Even if the Office has made a prima facie rejection of the claims, Applicant has presented sufficient evidence in the form of a Declaration of an expert in the field and journal articles published prior to the priority date of the instant patent application to overcome the rejection. The Office has improperly dismissed the evidence. The Office has failed to provide a proper factual or legal basis for dismissing the evidence.

All rebuttal arguments and evidence presented by Applicant must be considered by the Office. MPEP 2141 and 2145. The CAFC has repeatedly held that it is an error not to consider rebuttal evidence presented to counter a rejection. *In re Sullivan* Case No. 2006-1507, (Fed. Cir., Aug 29, 2007); *Sud-Chemie, Inc v. Multisorb Technologies, Inc.,* Case No. 2008-1247, (Fed. Cir., Jan 30, 2009). Applicant presented prior references as well as a Declaration that demonstrate the unpredictability of phosphorothioate linkages, which have not been suitably addressed by the Office. The Office asserts that Applicant's arguments were addressed in the prior Office Actions. Applicant respectfully disagrees.

In the Office Action date April 14, 2009, the Office has noted that several references have been listed in response to the Office Action; however, the Office has failed to adequately address the teachings presented in the references. Applicant presented a 1993 Science paper by Stein et al. (Science v. 261 p. 1004 1993) which shows that phosphorothioate modifications can have unpredictable effects on an oligonucleotide. In fact, phosphorothioate can unpredictably redirect oligonucleotide activity to create biological activity against targets where there previously was none. Phosphorothioate modifications have many more biological effects than simply reducing oligonucleotide degradation *in vivo*. As detailed in Stein et al., those effects were not well understood. For example, at p. 1008, col. 3 and p. 1009, cols. 1 and 2, four possible explanations

for the non-specific antisense effects of a particular phosphorothioate antisense oligonucleotide are described. Additionally Perez et al. (PNAS v. 21, p.5597-5561, 1994) teaches that one should use caution when considering oligonucleotides with phosphorothioate backbones because of the danger of nuclear transcription factor induction. In the Office Action dated April 14, 2009 the Office had not addressed these teachings of the cited references which clearly highlight the unpredictability of phosphorothioate modifications. In response to the Office Action dated April 14, 2009, Applicant pointed out to the Office that Applicant's rebuttal arguments concerning the Stein and Perez publications were not addressed. (Applicant Amendment dated July 14, 2009, pages 5-6). In the Office Action dated December 1, 2009, the Office has failed again to address Applicant's rebuttal arguments.

Had the Office considered the evidence of unpredictability presented by Applicant in the form of publications, the rejection should have been properly withdrawn.

Further, the Office failed to consider the Declaration evidence submitted with Applicant's Amendment dated March 12, 2009. Specifically, it is stated in the Office Action dated December 1, 2009, that the Declaration of Dr. Stein is not considered persuasive because

> " the motivation to combine references can be different than Applicants. Moreover the prior art does not indicate absolute predictability and also the prior art explicitly discloses the advantages of recited modifications as set forth supra. Furthermore, given the use of oligonucleotides comprising phosphorothioate backbone modification to improve stability of the oligonucleotide as being well known in the art leading to predictable results and hence their use is obvious under KSR." (Office Action dated December 1, 2009, page 8).

Even if the motivation to combine references is different than Applicant's motivation, the issue is irrelevant to the arguments presented in association with the Declaration of Dr. Stein. The Declaration was cited to establish the unpredictability of the combination, not the motivation to combine. The evidence presented in the form of a declaration clearly sets out that phosphate backbone modifications were, and still are, known to have unpredictable and undesirable effects on nucleic acids. (Stein 1, p12) They can change the shape of the molecule, they can alter the targets to which the molecule binds, and they can interrupt completely the binding of the nucleic acid to its target. (Stein 1, p12, 13, 14, 15, 17, 18, 19) One of ordinary skill in the art would have known that these unpredictable effects could alter or destroy the immune stimulatory capabilities of a CpG

nucleic acid. (Stein 1, p 24, 25) These aspects of phosphate backbone modifications were known well prior to 1994 and continued to be known to those of ordinary skill in the art through 1996.

The Office's assertion that the use of phosphorothioate modifications to improve stability of oligonucleotides "leading to predictable results and hence their use is obvious under KSR" is factually inaccurate. Presumably the Office is referring to the predictability of phosphorothioate modification of an antisense oligonucleotide. The primary reference cited in the obviousness rejection does not describe an antisense oligonucleotide. Rather the oligonucleotides described in the primary reference (Kuramoto et al) are immunostimulatory oligonucleotides. Whether the use of phosphorothioate modifications to stabilize the backbone of antisense oligonucleotides may be predictable is not determinative of whether the use of phosphorothioate backbone modifications would be predictable in the context of an immunostimulatory oligonucleotide. In fact, the Declaration of Dr. Stein, as well as the Stein and Perez et al publications described above are cited as positive evidence that such a modification is unpredictable. To conclude that that the use of phosphorothioate modifications to increase stability of any oligonucleotide would result in a predictable function of the oligonucleotide is factually incorrect. Based on this factually incorrect conclusion the Office improperly dismissed Applicant's evidence establishing that phosphorothioate backbone modification of an immunostimulatory oligonucleotide at the time of the priority date of the instant application was unpredictable.

Applicant notes that Dr. Stein was paid for his time in preparing and submitting the declaration in Interference No. 105,171.

Even if Applicant conceded that there was motivation to *try* to make a phosphodiester based immunostimulatory oligonucleotide resistant to *in vivo* degradation by modifying the phosphate backbone with a phosphorothioate, which it does not, it is clear that there would have been no reasonable expectation that such a modification would result in an oligonucleotide with the same immune stimulating properties, if retaining any immune stimulating properties at all. The nucleic acids of the claim must not only have a phosphate backbone modification, they also must be immunostimulatory. It is not enough to say that a phosphate modified nucleic acid could be made. Rather, an immunostimulatory nucleic acid having a modified phosphate backbone must be obvious from the references. This was simply not the case at the time of the claimed invention.

The Office has not articulated why the skilled person would have a reasonable expectation of success in making modifications to the Kurumoto et al oligonucleotide. General guidance as to expectation of success is not enough. At least some degree of predictability, determined at the time the invention was made, is required for obviousness. MPEP 2143.02. This is particularly true because, as noted above, phosphorothioates were known to cause many changes to the properties of oligonucleotides that may effect the activity of a phosphodiester oligonucleotide. Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories Inc., 520 F.3d 1358 (Fed. Cir. 2008)(when there are several unpredictable alternatives, it is not an "easily traversed, small and finite number of alternatives" that would support an inference of obviousness under KSR.)

Thus, the claimed invention was not obvious over the combination of cited references.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, the Director is hereby authorized to charge any deficiency or credit any overpayment in the fees filed, asserted to be filed or which should have been filed herewith to our Deposit Account No. 23/2825, under Docket No. C1039.70083US07.

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Respectfully submitted,

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